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ABSTRACT

The purpose of this theme issue is to review the basic physiological, nutritional, and pathological facts pertaining to the liver. It is an educational tool through which university teachers and people in charge of training may enhance their teaching programs. The main liver diseases seen in young children and pregnant women in tropical regions is reviewed. The liver plays a key role in supplying nutrition to the body, and is capable of delivering the elements needed by the different body tissues in the form of simple, immediately utilizable nutrients, such as glucose, amino acid, fatty acids, and vitamins. The liver is the coordinating center for all the biochemical machinery of the body. Knowledge of the physiology of the liver is essential in order to understand the mechanisms at work in the different disorders, so that adequate, effective solutions may be chosen to repair or prevent them. The first part of this booklet describes the functions of the liver cells and their role in the major metabolic processes involving carbohydrates, protein, lipids and vitamins. The second part of the booklet discusses disturbances in the form of the main syndromes or groups of clinical signs evidenced during liver diseases, and more specifically jaundice, portal hypertension, and hepatic comas. Information on the five forms of viral hepatitis is provided. The booklet also discusses abscess, cirrhosis, impairment, and tumors of the liver, and provides information on hydatic cysts and hepatocarcinoma. A discussion of liver alignments in pregnant women, which includes benign hepatic jaundice, acute steatosis, and jaundice concomitant with pregnancy concludes the booklet. Contains 15 references. (MOK)

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# CHILDREN IN THE TROPICS

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## THE LIVER, REGULATOR OF NUTRITION

1995 - N° 218

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ICC was created by the French government in 1949, on the initiative of Professor Robert Debré in particular, following negociations between France and the United Nations. Its purpose was to furnish those international and national agencies dealing specifically with child care with training facilities and educational and informational tools in the field of child health and development, viewing children within their family and surroudings.

As for its legal status, the International Children's Centre is a foundation under french law of recognized public utility, administered by an executive board with broad international membership.

ICC soon turned essentially toward Third World children and devoted its activities to the training and education of personnel with social, educational and administrative responsibilities as well as medical and paramedical workers.The desire for greater efficiency has led it to work increasingly with trainers and to concentrate its efforts on the methodological and educational aspects of mother and child care programmes.

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## THE LIVER, REGULATOR OF NUTRITION

❒ J.C. DILLON

1995 - N° 218

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# INTRODUCTION

In the course of childhood, as well as in adulthood, the amounts of food consumed by people daily vary enormously, so that the nutrient flow arriving in their tissues is also subjected to considerably day-to-day variations. At the same time, as we know, their nutrient requirements are relatively constant. The question, then, is how and where in the body does regulation take place, since it is this regulation that makes possible the harmonious development of children's growth, in spite of intermittent nutrient intakes.

There is only one organ that is equipped to ensure this marvellous regulation : it is the liver. It alone is capable of delivering the elements needed by the different body tissues in the form of simple, immediately utilizable nutrients ; that is, glucose, amino acids, fatty acids, vitamins, etc. The liver is the coordinating centre for all of the biochemical machinery of the body, and it is not at all surprising that in Ancient times the soul was believed to reside there.

In view of the key role played by liver in nutrition, it seems quite normal to devote an issue of Children in the Tropics to this subject, and particularly so since the environment in which children's development occurs in the tropical regions of the world makes heavy demands on their liver. These demands are of course linked to malnutrition and undernutrition, but also to aggressions by infections, be they of viral, parasitic or toxic origin.

We will therefore briefly review the basic physiological, nutritional and pathological facts pertaining to the liver. Knowledge of the physiology of the liver is essential in order to understand the mechanisms at work in the different disorders, so that adequate, effective solutions may be chosen to repair or prevent them. For this reason, the functions of the liver cells will be described first : that is, their role in the major metabolic processes involving carbohydrates, proteins, lipids and vitamins. Next, disturbances will be discussed, in the form of the main syndromes or groups of clinical signs evidenced during liver diseases, and more specifically jaundice, portal hypertension and hepatic comas. Last, the main liver diseases seen in young children and pregnant women in tropical regions will be reviewed.

# THE STRUCTURE OF THE LIVER

The liver is the largest organ in the body ; in adults, it weighs between 1,200 and 1,500 g, and represents about 2 % of the body weight, whereas in infants it may represent up to 5 % of body weight.

## Macroscopic description

The liver is a large-sized, brownish, smooth-surfaced organ surrounded by a thin capsule of connective tissue : it is situated on the right side, below the diaphragmatic dome (cf. figure 1). It is composed of two main lobes : the right lobe, which is larger and has the gallbladder located on its under side, and the left lobe.

The liver differs from other organs by the fact that it receives blood from two sources (cf. figure 2). The portal vein supplies it with blood from the stomach, pancreas and spleen, and above all from the intestine, so that it receives the nutrients taken in by the intestine before they pass into the general circulation. The hepatic artery enters it from the aorta, bringing in blood from the general circulation and supplying much of its oxygen, as well as those products of digestion that have travelled through the lymph vessels.

Intrahepatic circulation is composed of a network of sinusoidal capillaries receiving arterial afferents, which are branches of the hepatic artery, and venous afferents, branches of the portal vein.

It is the blood from the upper hepatic veins that drain the liver : these open into the inferior vena cava, which in turn goes to the right heart.

## Microscopic description

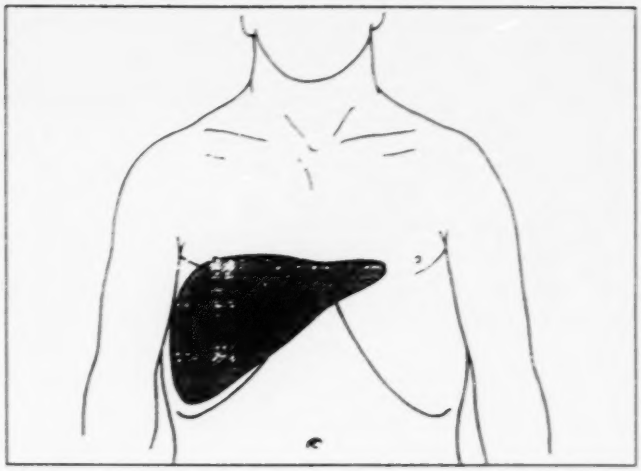
*The hepatic lobulus*

For histologists, the morphological unit composing the liver is the hepatic lobulus (cf. figure 3), which is made of radial rows of hepatocytes separated by a network of sinusoidal capillaries converging from the peripheral portal spaces to the interlobular vein. The rows of hepatocytes are composed of a single layer of cells. The hepatic lobuli are bordered by a thin layer of connective tissue, forming angles with the neighbouring lobuli, which angles, numbering approximately 6, are known as portal spaces. These portal spaces contain branches of the portal vein, the hepatic artery and the bile ducts.

The spaces between rows of hepatocytes are occupied by the sinusoidal capillaries, so that at least two sides of the hepatocyte are in contact with the blood stream. The endothelium lining these sinusoidal capillaries, as opposed to the lining of other capillaries, is extensively perforated. Here and there, larger cells are inserted between the endothelial cells : these are Kupffer's cells, and possess macrophage activity, meaning that they are able to capture and destroy certain undesirable substances, such as bacteria or food particles, that circulate in the blood within the portal vein.

*Figure 1 : Macroscopic view.*

*The liver, a large-sized organ located in the thoracic/abdominal area*



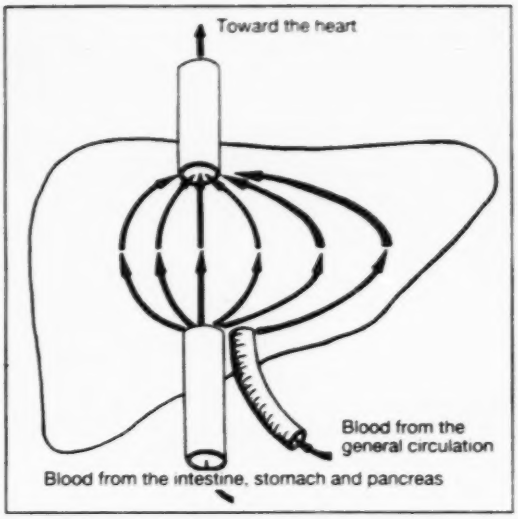



*Figure 2 : Circulation of blood in the liver.*

*The liver receives blood from the intestine, stomach, pancreas and spleen through the portal vein, a large blood vessel, and oxygenated blood from the general circulation, through the hepatic artery.*

*The mixed blood irrigates the liver through a network of capillaries known as the sinusoidal capillaries (see figure 3) and leaves the liver through the upper hepatic veins, to return to the general circulation and the heart.*

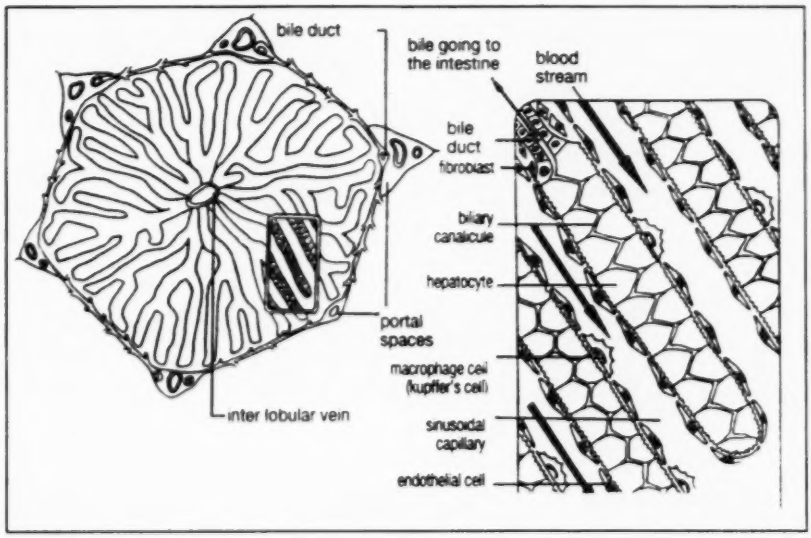



*Figure 3 : Ordinary hepatic lobulus. Histological appearance.*

*Microscopy reveals the polygonal structure of the hepatic lobulus, bordered by the portal spaces, with the interlobular vein in its centre.*

*When sufficiently magnified, the rows of hepatocytes may be seen, surrounded by the blood circulating in the sinusoidal capillaries. Thin canalicules are located between the rows of cells.*

*Bile*

Bile, produced by the hepatic cells, is excreted through minute ducts, the biliary canalicules, circulating in the opposite direction from the blood stream, and which open into the bile ducts in the portal spaces.

**Hepatocytes**

Hepatocytes, or hepatic cells, are large-sized cells with a vast cytoplasm that is granular-like, owing to its rich mitochondria content and endoplasmic reticulum. Electronic microscopy clearly evidences the presence of abundant intracytoplasmic glycogen, as well as of many lipidic vacuoles. The nucleus occupies from 5 to 10 % of the volume of the cell. The desoxyribonucleic acid (DNA) in the nucleus yields the information required for the synthesis of enzymes. Protein synthesis takes place in the ribosomes, and these function with the help of t-RNA, carriers of amino acids and of m-RNA from the nucleus.

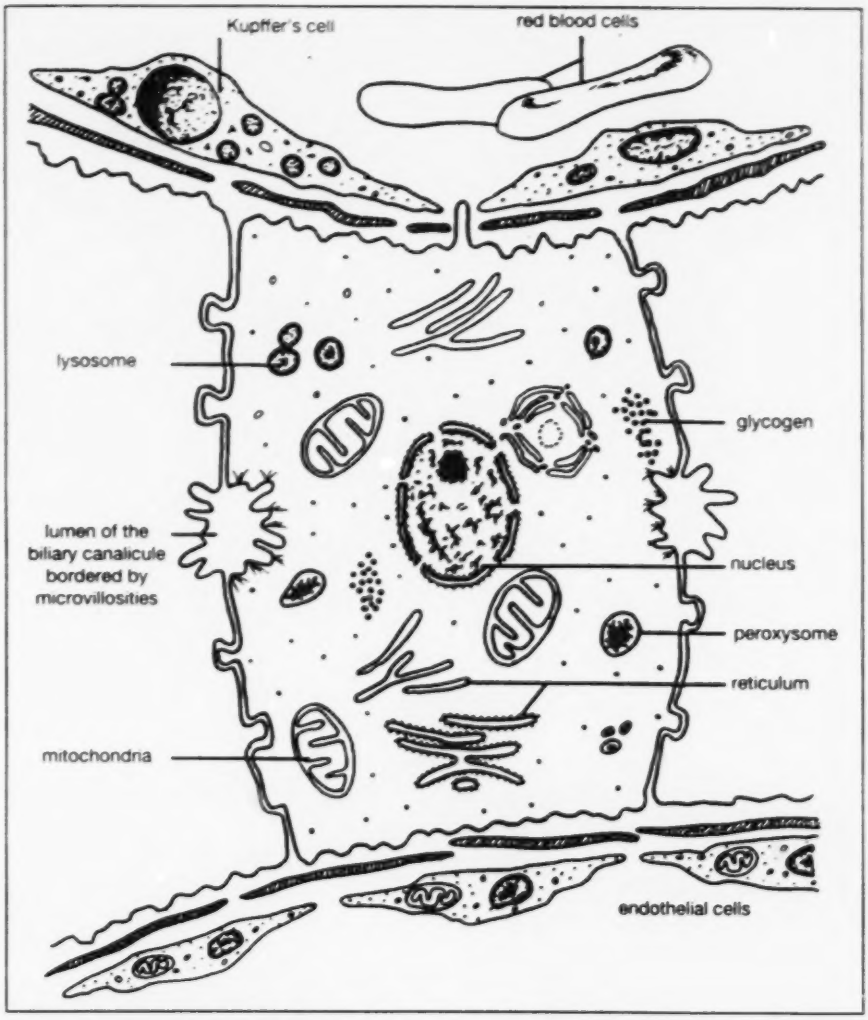



*Figure 4 : Ultrastructural appearance of hepatocytes.*

*Electronic mircroscopy shows the various components of the hepatocyte. They are : nucleus, mitochondria, lysosomes, peroxisome, the smooth and rough reticulum, and granules of glycogen.*

Mitochondria are extremely numerous in the hepatic cells : they provide the energy required for the metabolic processes, through the intermediary of the respiratory enzymes that catalyse the oxidation, by oxygen, of hydrogenated substrata, and make it possible to recover much of the energy released in the form of ATP.

Lysosomes, which are small, round bodies containing large amounts of hydrolytic enzymes, are involved in the degradation of unutilizable cellular substances.

The peroxisomes are equipped to achieve peroxidation through the use of various enzymes : catalases, oxidases for amino acids and an oxidase for uric acid.

The endoplasmic reticulum is the seat of a great many enzymes such as glucose-6-phosphatase, instrumental in releasing the glucose in glycogen, most of the enzymes involved in detoxification (including hydroxylases and mediating enzymes) as well as those inducing the synthesis of cholesterol and of lipids.

The cytosol also contains several major enzyme systems such as the one controlling glycolysis, through which glycogen is degraded into pyruvate, and another controlling glycogenesis, catalysing the opposite reactions for the formation of glycogen. It also contains the enzymes involved in the pentose cycles, and those participating in the metabolism of the various amino acids.

*Regenerative capacity*

The liver is composed of close to 300 billion hepatocytes. The life span of these cells is short - 300 to 500 days - after which they are replaced by the product of the cell division of a neighbouring cell. Their cell-regenerating capacity is characteristic of hepatocytes. In normal individuals, this capacity is so great that an average of one out of 1,000 hepatocytes is undergoing mitosis at any given time, in the absence of any disease. The liver therefore has an enormous ability to regenerate : further discussion of this will be found below.

The interplay between these different hepatic cell structures is what makes the liver capable of performing all of the metabolic functions described below.

**Clinical importance**

**When the liver is partially destroyed, as happens, for instance, following a viral infection (in viral hepatitis), the frequency of cell divisions increases ; this accounts for the spontaneously benign course taken by most cases of viral hepatitis, despite the extensive necrosis often attending them.**

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# THE LIVER IS THE CENTRAL ORGAN GOVERNING BIOCHEMICAL HOMEOSTASIS

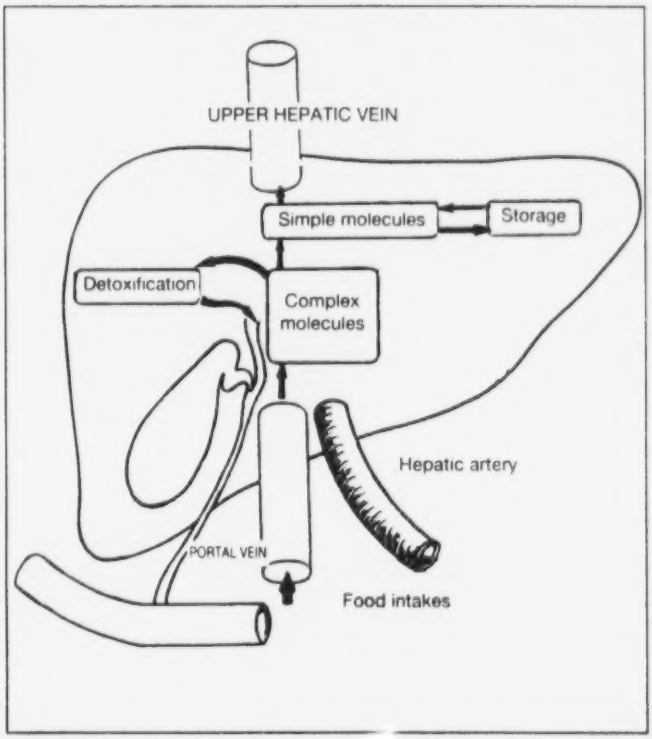


*Figure 5 : The main functions o. .ne liver.*

*The complex molecules from food are carried in through the portal vein and transformed into simple molecules that may easily reach the bloodstream through the upper hepatic veins. Some of these molecules may be stored in the liver, to be released as needed. The liver also takes care of detoxification of undesirable substances and their elimination through the bile.*

With its location between the digestive tract and the rest of the body, the liver, as mentioned above, is the coordinating centre for the entire biochemical machinery of the body. Thanks to its action, the different biochemical constants such as blood sugar, blood cholesterol and blood urea are maintained at their normal levels ; this is what is known as the body's homeostasis. The liver has been called «the biochemistry laboratory of the body», since it must constantly capture, transform, stock and distribute between the blood and the bile, the influx of nutrients that reach it through the alimentary tube. It is the organ that supplies nutrients to the various body cells, and in doing so it regulates almost all of the metabolisms, with several exceptions : certain minerals such as calcium and magnesium, as well as the acid-base balance of the blood. Furthermore, the liver is in charge of transforming foreign substances such as the toxins in the intestinal bacterial flora and the toxic pollutants vehicled to it with food. These varied functions are achieved by its multiple enzymes, which in turn are controlled by numerous hormones.

To carry out the many tasks it must perform, the liver requires a much greater metabolic potential than any other organ in the body. It must naturally be capable of deriving its own energy from the various substrata that reach it, and to do so it must possess enzymes for the degradation of carbohydrates and lipids. Like any other cell, hepatocytes must also be able to turn amino acids into proteins.

## Specific activities

In addition to these functions, however, the liver must be able to perform some specific activities, revolving around six basic tasks summarized below.

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*Bile production*

The liver produces bile, which is the external secretion of the liver. Bile contains some highly specific substances, the bile acids and bile pigments. The excretion of the bile acids represents the main means of eliminating cholesterol, but above all, these acids possess detergent properties which make them all-important for the digestion of fatty food. Bile pigments are essential for the elimination of bilirubin, a by-product of the degradation of haemoglobin.

*The transformation of molecules*

The liver transforms a variety of molecules produced during digestion into a limited number of other molecules capable of circulating in the blood stream and utilizable by most of the body tissues. It receives a variety of sugars contained in food (glucose, of course, but also fructose and galactose), and transforms them into a single circulating sugar, glucose.

*Regulation*

The liver regulates the concentration of these substances - of glucose, amino acids and circulating proteins (albumin), for instance, and of certain vitamins - in the blood. In the case of glucose, the maintenance of glycaemia at a set level is crucial for the satisfactory functioning of the brain : since it is unable to constitute reserves, the functioning of the brain depends entirely on a constant uptake of glucose, brought to it by the blood stream.

*Modification of metabolites*

The liver transforms endogenous metabolites such as cholesterol, the steroid hormones and bilirubin into soluble compounds easily excretable by the kidneys. These transformations call for many enzymes performing oxidation, reduction or hydrolysis.

*Detoxification*

The liver detoxifies substances that are foreign to the body - that is, xenobiotic - as well as medications. Given the huge number of such molecules and the extreme variety of their structure, the liver must possess different mechanisms for detoxification, so as to be able to adjust to each substance. It is a fact that the mechanism by which a pesticide residue present in food is transformed is in no way comparable to that involved in the transformation of a food colouring or an antibiotic : molecules are not identical, by any means !

*Purification*

The liver purifies the blood of circulating particles, and especially of germs ; this function is ensured by the Kupffer's cells surrounding the sinusoidal capillaries.

All of these functions are vital for the survival of the organism. Although they are extremely interdependent, they will be analysed separately.

The headings entitled «Clinical importance» provide some notions of hepatic pathology illustrating the importance of the liver's physiological functions by the outcome of their disturbance. «Nutritional importance» shows the dietary and nutritional conclusions to be drawn from an understanding of these general functions and of disturbances of them.

## THE LIVER AND THE METABOLISM OF CARBO-HYDRATES

In developing countries, where food staples are mostly cereal grains (rice, maize, wheat), roots (manioc) and tubers (yams), the daily diet yields large amounts of carbohydrates. Digestion of carbohydrate food releases hexoses - which are sugars with six carbon atoms - the most important of which, quantitatively speaking, are glucose, fructose and galactose. In the usual food ration, the largest quantities are represented by glucose, produced by the degradation of starch. Fructose, supplied by fruit and honey, and galactose, by dairy products, are present in smaller amounts. The other simple sugars, such as the pentoses, with their five carbon atoms, are quantitatively relatively minor.

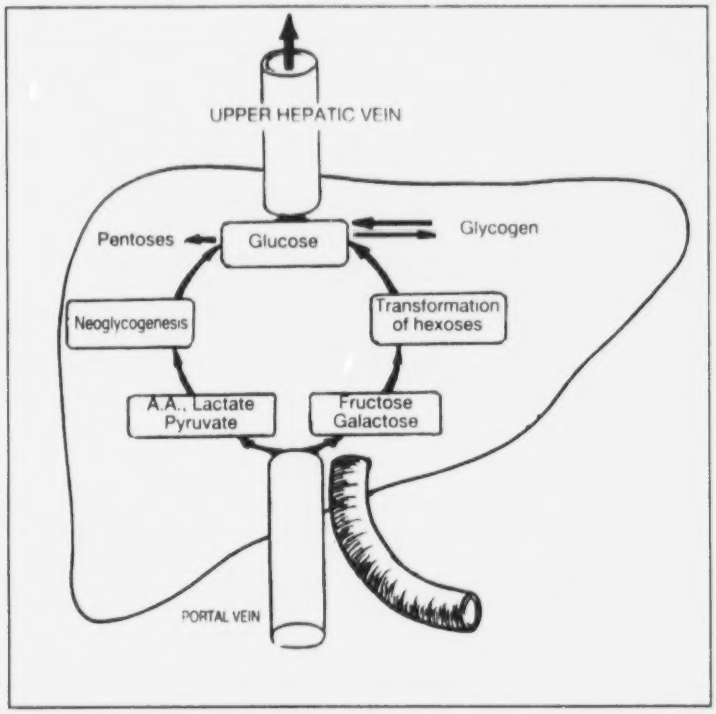


*Figure 6 : The role of the liver in the metabolism of glucose.*

*The hexoses coming in through the portal vein are transformed into glucose. Part of the glucose is formed from amino acids, lactate and pyruvate, by neoglycogenesis.*

*Some of the glucose enters the blood stream (maintaining the blood sugar concentration while another portion is stored as glycogen.*

We will discuss the destiny of the hexoses following their uptake in the intestine, then the mechanisms involved in the synthesis and degradation of glycogen in the liver.

The glucose coming from the intestine is mostly metabolized in the liver, while the rest is used by the peripheral tissues or converted into fats. This is also the case for fructose, much of which is used by the liver. Galactose, in turn, is metabolized exclusively by the liver.

### The destiny of hexoses

These three hexoses cross the liver cell membrane freely. Glucose immediately undergoes phosphorylation by a very active enzyme, glucokinase. Phosphorylation of fructose is ensured by a fructokinase. The metabolism of galactose is somewhat unusual. It is first phosphorylated into galactose phosphate (by a galactokinase), then into UDPgalactose (by a UDPgalactosyl transferase) and last, converted into glucose phosphate. The practical incidence (for pathology) of an understanding of these enzyme phases is discussed in another chapter.

### Synthesis/ degradation of hepatic glycogen

Following their conversion into glucose phosphates, the hexoses may participate in various reactions, and in particular in the transformation into glycogen, a polymer composed of molecules of glucose. The glycogenic function of the liver was discovered by Claude Bernard. As he was infusing a liver isolated from the body, Claude Bernard observed the occurrence of glucose in the efferent fluid. Several hours after the disappearance of the

glucose, resumption of the infusion again resulted in the presence of glucose in the efferent fluid. The liver therefore stores glucose in a polymerized form : glycogen. This polymer of glucose may be found in hepatic cells in large amounts, up to 10 % : it represents a stock of glucose available for restoring the blood sugar level if it happens to decline. If excess glucose is present in the blood, on the other hand, some of it may be converted into glycogen. However, the stock of hepatic glycogen is limited, and must therefore be continually reconstituted, an operation designated under the name of neoglucogenesis or neoglycogenesis. This neoformation of glycogen makes use of compounds such as lactate and pyruvate, formed in the tissues, as well as of certain amino acids, known to be glucogenic, such as alanine.

Both the synthesis and the degradation of glycogen are commanded by enzymes, which in turn depend on hormones produced outside of the liver. Certain hormones are hyperglycaemiating because they activate enzymes such as glucagon and adrenalin, that break down glycogen, or other enzymes such as cortisol, that produce neoglycogenesis. Still other hormones are hypoglycaemiating, since they stimulate glycogen synthesis ; this is the case of insulin. Between the production of glucose by the liver and its use by the body cells, then, many regulatory mechanisms are at work ; there are neurological mechanisms and hormonal mechanisms, but in any case all are delicate, and consequently fragile. This accounts for the great frequency of imbalances in carbohydrate regulation (such as diabetes) in human beings.

**Nutritional importance**

Glucose produced in the liver is the only source of blood glucose other than that found in food. Blood glucose is vital for both the nerve and red blood cells, for which it is the primary nutrient. Fortunately, the liver is able to make glycogen from a multitude of elements - various carbohydrates, glycogenic amino acids, lactate, pyruvate, etc. - this is what is known as neoglucogenesis. Neoglycogenesis is an extremely intense phenomenon, since adults are capable of producing up to 420 g of glucose daily ! This mechanism explains why blood glycaemia levels may remain normal in individuals with an insufficient dietary carbohydrate intake : this is the case during complete fasting, or for Eskimos, who eat mostly lipids and proteins. When carbohydrates are completely eliminated from the diet, neoglycogenesis relies on the body's amino acids, and is performed at the expense of the muscles, which contain the largest bodily reserves of these.

It is the mechanism of neoglycogenesis using the muscular amino acids that accounts for the spectacular melting of muscle observed in children with major dietary deficiencies, following surgery for instance, before the child resumes eating, or during prolonged fasting following an infectious disease. Fortunately, after a few days of fasting the brain, a heavy consumer of glucose, becomes capable of consuming another source of energy : the ketone bodies, which will be discussed further down. Consumption of ketone bodies reduces glucose consumption and consequently the need for amino acids, which in turn moderates the melting of muscle during complete fasting.

**Clinical importance**

Certain enzymes involved in the metabolism of glycogen may be lacking at birth ; in this case, glycogen accumulates in the liver, a condition known as glycogenosis. Such glycogenosis is a typical storage disease of the liver, taking the form of considerable hepatomegaly, often connected with hypoglycaemia.

The congenital absence of enzymes involved in the metabolism of galactose results in congenital galactosaemia, evidenced in neonates by symptoms of severe hepatic insufficiency and in small children by hepatomegaly associated with a cataract and retarded psychomotor development.

In infants, hereditary fructose intolerance results in signs of hypoglycaemia, along with vomiting, following a fructose-rich meal.

In the last analysis, the maintenance of the supply of energy required by the organism depends on the ability of the liver to regulate the metabolism of carbohydrates - as well as of lipids, as will be seen further down. It is the liver that enables the body to cope with the alternation of periods of abundance and shortages.

## THE LIVER AND THE METABOLISM OF AMINO ACIDS AND PROTEINS

One vital function of the liver is its constant maintenance of the plasmatic amino acid levels at concentrations adequate for ensuring the synthesis of proteins in all of the body cells. It is estimated that the liver of an adult weighing 60 kg and eating a diet with a normal protein content supplies approximately 106 g of amino acids to the different tissues each day : that is, 50 g of amino acids for the intestine (to replace desquamated intestinal cells and supply the digestive enzymes), 28 g for the synthesis of red blood cells and leukocytes, 20 g for the pancreas (for the synthesis of the pancreatic enzymes) and 8 g for the muscles.

At the same time, the liver must be able to cope with any excessive intake of amino acids : that is, it must be capable of breaking these down. To do so, it possesses the enzymes required for the catabolism of surplus amino acids.

This ability both to synthesize and to break down means that the liver is the regulatory organ in charge of adjusting the distribution of amino acids to the body's needs for the synthesis of proteins.

### Essential and non-essential amino acids

In the course of their evolution, higher animals, including human beings, have lost the ability to synthesize half of the 20 amino acids that make up proteins (valine, leucine, isoleucine, phenylalanine, tryptophan, lysine, histidine, threonine and methionine), so that intake of these amino acids has become essential, and they absolutely must be supplied by their diet. In micro-organisms and plants, the synthesis of these amino acids, called essential amino acids, is a complex mechanism requiring numerous enzyme phases. By the fact that it does not synthesize these essential amino acids, the human organism economizes on the need to produce a considerable number of enzymes but in

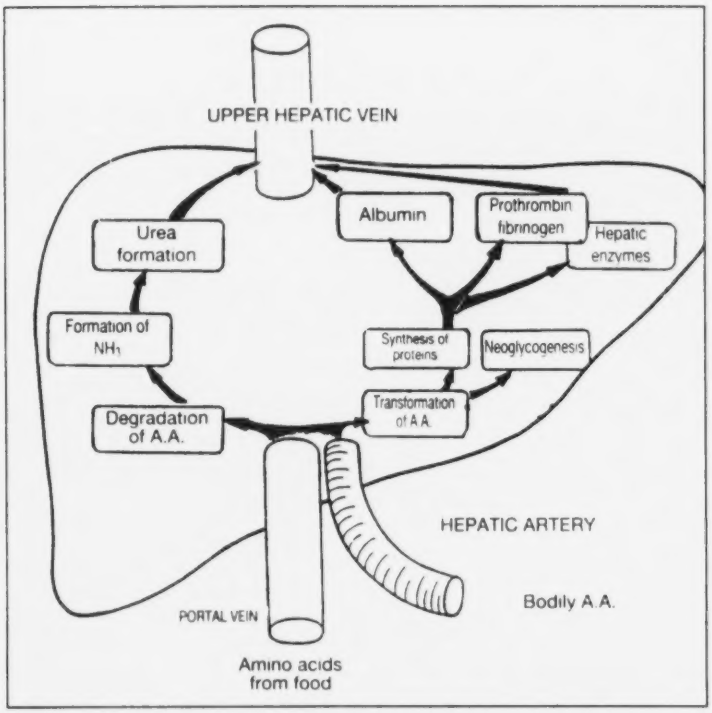


*Figure 7 : The role of the liver in the metabolism of proteins*

*The amino acids derived from food and from the body tissues are mostly transformed locally, the rest is degraded.*

*Transformation of amino acids is required for the synthesis of proteins, and if necessary for the formation of glucose, by neoglycogenesis. Certain proteins such as albumin, prothrombin and fibrinogen are sent into the blood stream, while others such as the enzymes do not leave the cells.*

*The degradation (catabolism) of surplus amino acids leads to the formation of urea, which goes from the liver to the kidneys.*

return it becomes dependent on the uptake of these essential amino acids, found in the environment. Human beings have become extremely vulnerable to any shortages in intakes.

While the ability to synthesize the essential amino acids has been irremediably lost, the synthesis of non-essential amino acids (arginine, proline, glutamic acid, glutamine, aspartic acid, cysteine, tyrosine, serine, glycine and alanine) is performed simply, through a limited number of reactions based on intermediate metabolites. The liver has no difficulty in supplying non-essential amino acids regularly, then, whenever they are needed for the synthesis of body proteins.

## Reactions involved in the transformation of amino acids

The main reaction involved in the synthesis of non-essential amino acids is the transferral of the amino group, whence the name of the reaction : transamination. The enzymes that perform this reaction are called transaminases. Two of them are particularly important in medicine : alanine aminotransferase (ALAT) and aspartate aminotransferase (ASAT).

**Clinical importance**

**The assay of transaminases in the blood is of great diagnostic value in the course of liver diseases, inasmuch as these enzymes easily leave the liver cell during certain ailments such as viral hepatitis. The latter disease produces cell necrosis (cytolysis) : the presence of these enzymes in the blood is therefore a sign of a damaged liver.**

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## Destiny of the carbon skeleton of essential amino acids

All amino acids are catabolized in the liver, with the exception of the branched-chain amino acids (valine, leucine and isoleucine) that are catabolized in the muscles since the specific transaminases for these branched-chain amino acids are found in the muscles only and never in the liver.

The carbon skeletons are converted either into glucose (glucogenic amino acids) or into acetyl-coA (ketogenic amino acids) ; these are then stored in the liver, in the form either of glycogen and/or of triglycerides. Through a series of complex reactions, most of them are later converted into intermediate metabolites that intervene during the Krebs cycle. Thus, any surplus essential amino acids provided by the diet are used to supply energy.

## End products of nitrogen metabolism

The carbon skeleton is transformed into energy, then, as we have seen : but what becomes of the nitrogenous radicals, $NH_2$, of which the body must rid itself in one way or another ? One might think that they would be eliminated in the form of $NH_3^+$ ions, but these ions are toxic. The form actually used is urea : urea is a highly diffusible, highly water-soluble substance, and is therefore easily excreted in urine. The transformation of $NH_2$ radicals into urea takes place in the liver (and in the liver only), through a series of four successive reactions described by Krebs and named cycle of urea, or Krebs-Henselheit cycle.

**Nutritional importance**

**In case of excessive protein intake (in meat-rich diets, for instance), the liver is well equipped to catabolize the surplus amino acids and to reject the nitrogen in the form of urea (when the state of the kidneys allows this, at any rate). The carbon skeleton of these amino acids is converted into carbohydrates (glycogen), lipids (triglycerides) or directly into energy. This explains why the caloric value of proteins within the body is just as high (4 Kcal/g) as that of carbohydrates (4 Kcal/g).**

## Synthesis of circulating proteins by the liver

The liver releases large amounts of proteins into the blood stream every day. Indeed, it synthesizes practically all of the plasmatic proteins, with the exception of the immune globulins. The amount of albumin produced daily is estimated at 12 g, while the amounts of the other plasmatic proteins are estimated at 5 g a day (alpha 1 anti-trypsin, haptoglobin, carrier proteins such as retinol-binding protein, transferrin, ceruloplasmin, the proteins involved in inflammatory reactions and coagulation factors).

**Nutritional importance**

**In childhood protein energy malnutrition, the synthesis of albumin is reduced, for lack of amino acids : assay of blood albumin is therefore a good indicator of the protein nutritional status, as is the assay of retinol binding protein, or RBP.**

**Clinical importance**

Emphasis should be placed on the pro-coagulant proteins : fibrinogen, prothrombin, proaccelerin, proconvertin, Stuart's factor and anti B haemophilic factor, and it should be remembered that coagulation of the blood depends on the correct functioning of the liver. Actually, when early signs of inadequate functioning of the liver are sought, laboratory confirmation of disturbance of the coagulation factors is sufficient evidence.

In addition, the liver synthesizes a great many enzymes for its own metabolic needs. To do so, it extensively reutilizes those amino acids resulting from the degradation of these protein-enzymes, the half-life of which is short, and which are degraded locally in the lysosomes.

Since amino acids are so important for the proper functioning of both the liver and the organism, what happens in case of protein fasting ? In case of total protein fasting (following surgery, for instance), the liver makes use of the proteins contained in the muscles to supply the amino acids required for its various syntheses ; that is, for the production of red and white blood cells, the replacement of the intestinal mucosa, the production of digestive enzymes and of serum proteins. This explains why total deprivation of proteins and lowered blood albumin are accompanied by melting muscles.

*To sum up*

In order to maintain protein synthesis within the body, the liver requires a constant supply of the essential amino acids. This is why children's diet must contain these essential amino acids in amounts sufficient for the occurrence of the normal growth process (requirements for the synthesis of proteins) and for a satisfactory nitrogen balance.

Furthermore, this intense hepatic activity requires a sufficient energy intake. The adult liver consumes an estimated 480 Kcal daily, representing 27 % of the basal metabolism. Clearly, then, any energy deficiency affects the metabolism of proteins, the clinical outcome of which is protein energy malnutrition. And even if the essential amino acid intake is relatively sufficient, an energy deficiency causes muscular catabolism and a negative nitrogen balance.

**These basic notions concerning the functioning of the liver explain why the prevention of childhood malnutrition requires the simultaneous administration of proteins and energy. Nutritionists have too long exclusively placed emphasis on the primordial need for proteins, leading to the search for new sources of protein (such as yeasts and spirulins) to be fed to undernourished children. The fact is that these expensive proteins are converted into energy, and therefore wasted, to satisfy the body's need for energy, which receives priority. Instead, children should be given a mixture that is sufficiently rich in energy : often the enrichment of grain foods by the addition of oil, or the prior hydrolysis of the starch in cereal grains is recommended so as to improve the energy density of weaning foods. The simultaneous administration of adequate amounts of the essential amino acids is important here.**

## THE LIVER AND THE METABOLISM OF LIPIDS

The lipids contained in food are of three types : triglycerides, phospholipids and cholesterol.

Triglycerides are neutral fats : they are the form in which energy is stored in both animals and plants ; they represent over 95 % of dietary fats. An example of a phospholipid is the lecithin in egg yolks. Cholesterol is present in the cell walls of animal foods.

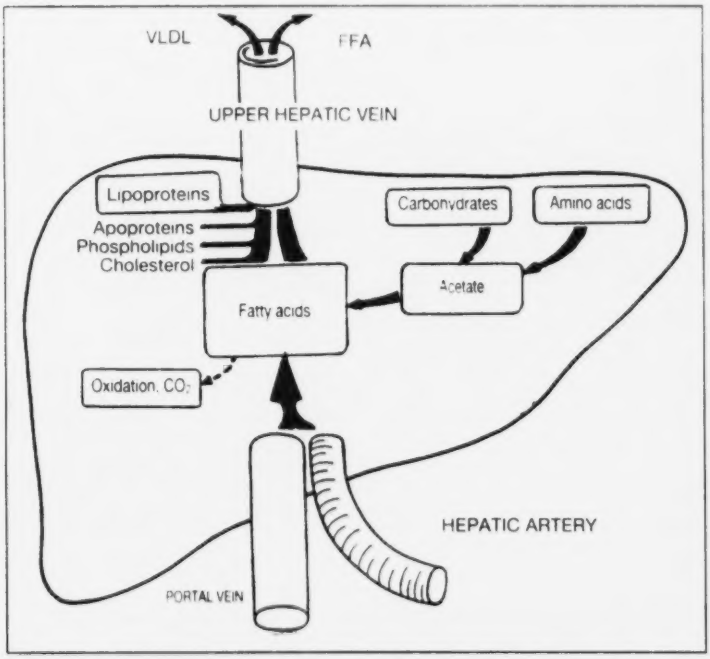


*Figure 8 : The role of the liver in the metabolism of lipids.*

*The fatty acids come from food (through the portal vein), from the fatty tissues (through the hepatic artery) or are formed in the liver from carbohydrates or amino acids (via acetate). They may take three courses : oxidation in the liver, for the satisfaction of its energy requirements, exportation to the blood in the form of free fatty acids (FFA) or exportation in the form of VLDL lipoproteins following incorporation of cholesterol, phospholipids and an apoprotein.*

Practically all of the lipids eaten travel to the liver. Some go there directly, through the portal vein : these are medium-chain triglycerides and some fatty acids. However, most of the dietary lipids travel through the digestive (chyliferous) lymph ducts in the form of droplets of fat : these are the chylomicrons, that are stored in the fatty tissue. They are later released into the general circulation as needed by the body, and then arrive in the liver through the hepatic artery.

Furthermore, the hepatocytes themselves are able to synthesize practically all of the fatty acids, with the exception of two of these : arachidonic acid and eicosapentaenoic acid. Since these two are not synthesizable, they are considered essential for human beings, and must be present in the diet. Their foremost feature is the fact that they are necessary for the synthesis of compounds such as the prostaglandins, required for the proper functioning of the organism.

Irrespective of how they reach the liver, by the portal or the lymphatic route, or by on-site synthesis in the hepatocytes, lipids serve a number of purposes within the liver. These are discussed below under eight headings.

*Supplying energy*

Lipids supply the liver with energy for its own specific needs. An estimated 75 % of the energy utilized by the liver comes from the oxidation of lipids : the liver is therefore a major consumer of fats. It possesses all of the enzymes needed for their oxidation and transformation into ATP in the mitochondria. Under normal conditions, the liver does not store fats.

*Production of free fatty acids*

The liver produces circulating fatty acids known as free fatty acids (or FFA) that are the preferred energy for fuelling muscles (including the heart muscle). It is a fact that in itself, blood sugar (1 g/l) is insufficient for supplying sufficient amounts of energy to

the muscles ; the organism must necessarily synthesize fatty acids for the fulfilment of these needs. Most of these FFA are bound to albumin for transportation in the blood. The liver is therefore in charge of both producing the FFA and ensuring their transportation by the blood.

*Synthesis of cholesterol*

The liver synthesizes cholesterol, a substance that is necessary to life, since it is a precursor of the steroid hormones, vitamin D and the bile salts. Although cholesterol is generally available in the food ration, many body tissues are capable of synthesizing it. Because of its size, the liver plays a major role in the daily synthesis of cholesterol. In fact, the cholesterol that is not used by the peripheral tissues is taken back into the liver, so that the latter is involved in the balance between the intakes, synthesis, metabolization and biliary secretion of cholesterol.

*Synthesis of bile acids*

The liver converts a large percentage of the cholesterol it produces into bile acids. In adults, between 500 and 700 mg of these bile acids - cholic and desoxycholic acid - are produced daily. Next, these acids are conjugated with amino acids (glycine and taurine) before being excreted in the bile. The bile salts are indispensable for the emulsifying of dietary fats in the duodenum. The liver avidly reabsorbs them, so that sufficient amounts will always be available at mealtimes : this cycle is described as the entero-hepatic bile salts cycle. If insufficient quantities of bile salts are produced, the uptake of fats is inadequate and they may be found in the faeces (this is steatorrhoea).

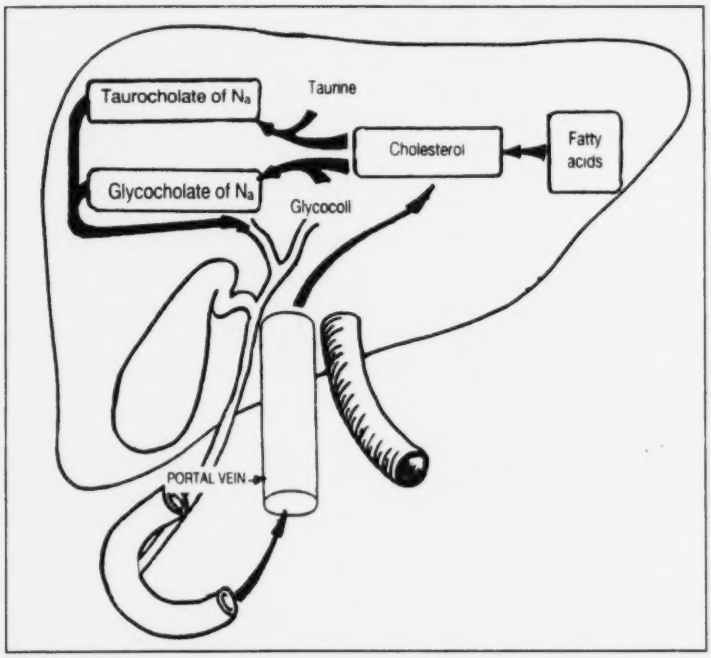


*Figure 9 : Metabolism of cholesterol, formation of bile acids and salts.*

*A fraction of the cholesterol is oxidized into cholic and desoxycholic acids (not shown here). These acids are conjugated with taurine and glycocoll to from the bile salts. Taurocholate and glycocholate are excreted through the bile ducts. They are partially reabsorbed into the intestine and return to the liver (this is the entero-hepatic bile salts cycle).*

The liver is in charge of synthesizing and exporting the various lipids (triglycerides, phospholipids and cholesterol) to the peripheral tissues, in the form of lipoproteins, because these lipids are insoluble in the blood, and therefore untransportable as such. They must be bound to a protein (an apoprotein) to form a lipoprotein, which is then soluble in the blood plasma. Because of the triglycerides bound to them, these lipoproteins are very light and are therefore known as very low density lipoproteins, or VLDL. The blood concentration of VLDL rises after meals, thanks to which energy and cholesterol may be distributed to the peripheral tissues.

**Clinical importance**

Cholesterol is transported to the tissues in the form of VLDL lipoproteins, and the unused part is returned to the liver by LDL lipoproteins, which are then bound to well-identified receptors located on the surface of the hepatocytes. If these receptors are not synthesized because of a genetic defect, extremely high blood cholesterol levels may ensue, producing early atherosclerosis in small children (this is familial hypercholesterolaemia).

*Production of ketone bodies*

During periods of fasting, the liver produces ketone bodies (aceto-acetic acid and beta-hydroxybutyric acid) : these represent the form of energy most easily made available to tissues, and to the brain in particular. This is because the coefficient of water-solubility of these ketone bodies is higher than that of fatty acids.

*Metabolism of the steroid hormones*

The steroid hormones synthesized from cholesterol, such as the adrenal cortex hormones (cortisol, aldosterone and the adrenal androgens), the male hormones produced in the testicles, oestrogens and the progestational hormones are all partly dependent on the liver, since it supplies cholesterol to the endocrine glands ; but only partly so, since cholesterol is also produced in the endocrine gland itself. The liver is mostly active in the catabolism of these substances : the hormones are eliminated in the urine following their reduction and conjugation (mainly glycuronic conjugation). Mention should be made of the anti-diuretic hormone, much of which is also destroyed in the liver. Half of the insulin produced by the pancreas is believed to be destroyed by the liver. The role of the liver in the metabolism of fat-soluble vitamins will be discussed further down.

**Clinical importance**

The liver does not store large amounts of lipids, and it has small reserves, then, as opposed to carbohydrates, large quantities of which are stored as glycogen. Lipid deposits - that is, hepatic steatosis, is always an indication of a poorly functioning liver, as is often the case in chronic alcoholic intoxication.

**Nutritional importance**

If lipid intakes are insufficient, as is the case for some children in Bangladesh, whose food ration hardly provides more than 5 g of fat a day, the liver continues to produce the lipids required for the proper functioning of the body. However, it is unable to synthesize the essential fatty acids, and especially arachidonic acid, daily requirements of which are in fact extremely low. Do these children run a risk of deficiency ? The studies conducted so far - in India in particular - do not show this to be the case, given the present possibilities of biological investigation, at any rate. Nonetheless, it does seem wise to comply with international recommendations suggesting the enrichment of infant foods with small amounts of linoleic acid.

Severe protein deficiencies (kwashiorkor) cause defective synthesis of lipoproteins, the carrier proteins transporting fats such as albumin, the consequence of which is fatty infiltration of the liver. Hepatic steatosis in kwashiorkor should therefore be treated by the administration of dietary protein rather than by a hypolipidic diet. In children, quite fortunately, the liver resumes its normal activity following nutritional rehabilitation, and does not suffer from any adverse after-effects.

## BILE AND THE EXCRETORY FUNCTION

Aside from its metabolic functions, the liver also has excretory functions : it rejects certain undesirable substances into the intestine, with the help of bile. Bile is secreted directly by the hepatic cells into the biliary canalicules located between the rows of hepatic cells, and from there into the bile ducts, after which it travels to the gallbladder and duodenum. Bile is secreted constantly by the hepatocytes (about 0.7 litre a day), but does not flow continuously into the intestine : between meals, the constrictor muscle (Oddi's sphincter) closes the place where the common bile duct enters the duodenum, preventing bile from flowing out and thus causing it to accumulate in the gallbladder, where it is concentrated to 1/5th or 1/10th of its volume. This bile concentrate in the gallbladder yields, in a small volume, large amounts of the components of bile required for digestion. When the body is ready to digest and needs bile, the gallbladder contracts and its content is mixed with the duodenal chyme. The contraction is activated by a reflex and with the help of a hormone (cholecystokinin). In addition to the lipids in the chyme, egg yolk and magnesium sulphate constitute particularly effective stimuli for the secretion of cholecystokinin (that is, they are cholagogue substances). Further, the secretin and the bile salts contained in the blood stimulate bile production in the liver (they are choleretic substances).

### THE COMPONENTS OF BILE

Aside from water and electrolytes, the components of bile are organic compounds : bilirubin, the bile acids, cholesterol and phospholipids (lecithin). Some medications may also be excreted with bile, as will be seen further down.

### Bilirubin

Bilirubin, 85 % of which is the product of the degradation of red blood cells, is an essential component of bile. The degradation of haemoglobin (mostly in the macrophages) causes it to split into the components of globin and iron, successively yielding the formation of biliverdin and bilirubin (35 mg of bilirubin for 1 g of haemoglobin). Free bilirubin has a low level of water-solubility and its fat-solubility makes it toxic for the tissues ; it is therefore bound to albumin in the blood (2 mols of bilirubin for 1 mol of albumin), but is taken into the hepatic cell without its albumin. The use of glucose, ATP and UTP leads to the formation of UDP-glucuronide, which is conjugated with bilirubin through the action of an enzyme, glycuronyl transferase. This detoxification mechanism leads to the formation of conjugated bilirubin, a water-soluble substance actively secreted into the biliary canalicules. Bilirubin is degraded in the intestine into urobilin and stercobilin, both

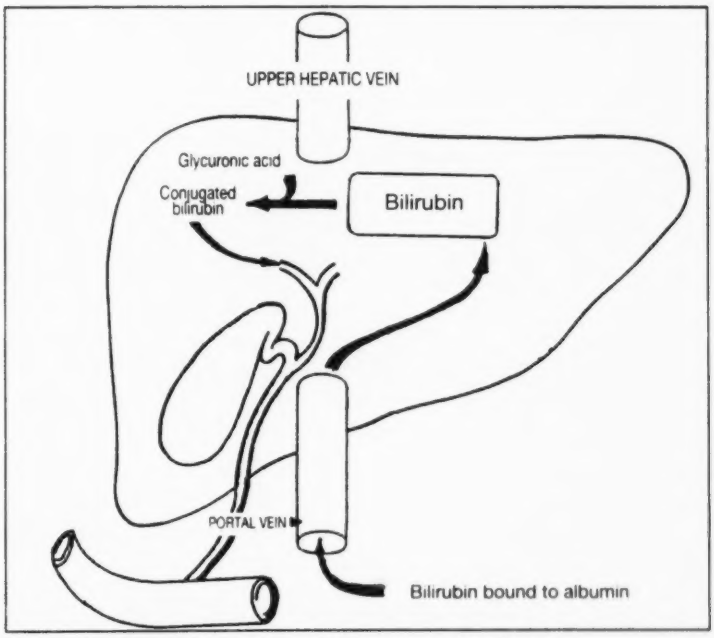


*Figure 10 : Transformation of bilirubin in the liver.*
*Bilirubin, a product of the degradation of haemoglobin, reaches the liver bound to albumin. It then combines with glycuronic acid, to form what is known as conjugated bilirubin, which is excreted through the bile. Part of it escapes glycuronic conjugation and enters the bloodstream.*

evacuated in the faeces. However, some of the bilirubin escapes glycuronic conjugation and reaches the general circulation ; it is excreted by the kidneys. Normally, the blood bilirubin concentration is between 3 and 10 mg/l. When this concentration exceeds approximately 18 mg/l, the ocular conjunctiva and later, the skin, turn yellow : this is jaundice.

**Clinical importance**

Jaundice, or icterus, occurs when bilirubin crosses into the blood, and is therefore an indication of a disturbance of the liver cells, the most frequent cause of which is the destruction of these cells by a virus (in viral hepatitis), or the obstruction of the bile ducts outside of the liver (by a gallstone or malignant tumour).

In neonates, the glycuronic conjugation function is not completely developed at birth, whereas bilirubin production is considerable. Neonatal jaundice is therefore a normal occurrence : called physiologic jaundice of the newborn, it peaks between the 3rd and the 5th day, and disappears at age 10 days. Neonatal jaundice is benign in itself, but the situation may become dramatic if the «physiological» inability to evacuate bilirubin is compounded by another cause of jaundice, and especially by the accelerated destruction of red blood cells because of a Rhesus incompatibility between mother and child. Bilirubin then crosses the encephalo-meningeal barrier and is deposited in the central grey nuclei of the brain ; this is called nuclear jaundice or kernicterus. If left untreated, those children who do not die within a few weeks retain permanent neurological sequelae affecting their motor, sensory and intellectual development.

Neonatal hyperbilirubinaemia may be prolonged and accentuated in some breast-fed infants. This jaundice is believed to be linked to enhanced reabsorption of the pigment, in connection with the high glycuronidase content of breast milk, which increases the amount of free bilirubin found in the contents of the child's intestine. Despite their jaundice, these children develop normally and their general health is good : there is no need to discontinue breast-feeding, and jaundice disappears without treatment within 3 to 10 weeks.

**Nutritional importance**

Diet itself never has a decisive influence on jaundice. It would be a serious mistake to discontinue breast-feeding in an infant with jaundice.

## Bile acids

The bile acids (cholic and desoxycholic acids) are synthesized by the liver from cholesterol. This synthesis is controlled by the amount of bile salts reabsorbed at the intestinal level (the entero-hepatic bile salts cycle). In the liver, the bile acids are conjugated with a sulphurated amino acid, taurine, for 1/3, and with another amino acid, glycine, for 2/3. They are then secreted continuously into the bile in the form of sodium salts (tauro and glycocholate of sodium) and stored in the gallbladder between periods of digestion. With the arrival of the bolus in the duodenum, the bile is expelled, and the bile salts cross into the intestine.

The bile salts play a most important role in the digestion of fats, since they are needed for the emulsion of dietary lipids and the reduction of the size of lipid molecules, which increases the surface affected by pancreatic lipase. The combined action of

pancreatic lipase and of the bile salts produces the hydrolysis of dietary triglycerides into fatty acids and their immediate absorption by the intestinal mucosa. The bile salts present in the intestine are reabsorbed and return to the liver, and so are not lost. They are recycled, then, through what is called the entero-hepatic circulation of bile salts. It is estimated that the pool of bile salts goes through its cycle from 6 to 10 times a day.

Bile salts have other effects as well : they stimulate iron and calcium uptake, prevent coagulation of the intestinal mucosa by inhibiting mucinase, activate peristaltism in the small intestine and facilitate defecation. They also have a bacteriostatic action, since they combat the pullulation of aerobic germs, and last, they have a choleretic action.

**Nutritional importance**

In infants, if a malformation of the bile ducts (atresia of the bile ducts) prevents the bile salts from reaching the intestine, the breast milk lipids are not absorbed : this rapidly causes a deficit in energy and fat-soluble vitamins, and therefore, malnutrition. These children require special nutritional care.

## Cholesterol

Cholesterol is practically not soluble in water, and is therefore «dissolved» in the bile, with the help of the phospholipids and bile salts. The role of biliary cholesterol has not been sufficiently elucidated. Given its low concentration in bile, it cannot be an emunctory of the cholesterol produced in the liver. It is interesting to note that the elimination of cholesterol in the bile is neither quantitatively important nor directly connected with the blood cholesterol level.

**Clinical importance**

Modifications in the proportions of the mixture of these three substances - cholesterol, phospholipids and bile salts - may result in the precipitation of crystals of cholesterol : this is one cause of the formation of gallstones, or calculi. These are formed in the gallbladder and may migrate along the bile ducts, producing bouts of hepatic colic.

**Nutritional importance**

Prevention of the formation of calculi requires action affecting three factors simultaneously : the concentrations of cholesterol, bile salts and phospholipids in the bile. In itself, reduction of the dietary cholesterol intake cannot eliminate gallstones ; there is no diet that combats already existing lithiasis.

However, calculi are known to develop more frequently in obese individuals, whose bile is often oversaturated with cholesterol, and also in individuals with hypercaloric, fat-rich diets. Prevention of the precipitation of gallstones therefore involves the prescription of a diet moderately rich in calories and lipids. A diet rich in plant fibre somewhat decreases the cholesterol saturation of bile, and may have some preventive effect on the formation of calculi.

## THE DETOXIFICATION FUNCTION

*Mechanisms of transformation*

The liver possesses mechanisms capable of combating a great many useless or toxic substances, by making them harmless and eliminating them through the bile. These substances may be endogenous, such as the skatole and indole produced by intestinal fermentation, or exogenous, including medications and environmental toxins. To do so, the liver possesses several mechanisms of transformation. First, oxidation occurs, after which OH or COOH groups may be bound to the molecule to be eliminated ; at this point, these groups may be bound either to a glycuronic acid (in the glycuronic conjugation of chloramphenicol, for instance), a sulphate (conjugated sulphates), an acetate or some amino acids. As mentioned above, glycocoll and taurine are active in the transformation of bile acids into bile salts. Conjugation also serves to inactivate and solubilize a great many substances.

Other metabolic transformations are also possible. They include dehydrogenation, acetylation and methylation, which inactivate all sorts of drugs. Some of the enzymes involved are elicited in the liver by the drugs themselves (one example being phenobarbital) : this means that their administration enhances the activity of these enzymes, including their activity with respect to substances other than the drug itself. For instance, small doses of phenobarbital may be administered to infants with excessive free hyperbilirubinaemia, so as to induce glycuronyltransferase and cause the jaundice to recede more rapidly.

*Faecal excretion*

The substances formed during the metabolic transformations described above are actively secreted into the bile and reach the intestine, from which they are evacuated in the faeces.

*Urinary excretion*

A second mechanism, using glutathione as acceptor, is involved for substances to be excreted in the urine. Specific enzymes combine certain toxic or cancerous substances such as chloroform, the epoxides, naphthalene and phenanthrene with glutathione - another amino acid. These compounds are then excreted by the kidneys in the form of mercapturic acids.

### Alcohol

Alcohol, undeniably the xenobiotic most widely consumed by human beings, undergoes a most peculiar type of detoxification. The liver has three enzyme systems for the oxidation of ethanol into acetaldehyde : the foremost of these involves an enzyme, alcohol dehydrogenase, relayed by a system of P450 cytochromes and a catalase. Despite the existence of these enzyme-powered detoxification systems, the capacity of the liver to metabolize alcohol remains limited.

The cytochrome system is known to be partially inducible, which means that its capacity increases when the substrata, ethanol, is consumed regularly ; this accounts for the alcohol tolerance of some heavy drinkers. Another known fact is the tremendous individual differences in hepatotoxic reactions to alcohol. All of these facts illustrate the difficulty in determining when drinking becomes dangerous, and in formulating concrete recommendations. The difficulty is further compounded by the fact that toxicity is definitely increased by the nutritional disorders induced by alcohol consumption itself.

Be this as it may, beyond a given figure for maximum daily intake, which varies from one individual to another, alcohol is no longer transformed in the liver, and it circulates to the other organs. The regular, steady consumption of alcohol causes overloading of the liver with lipids (hepatic steatosis), followed by fibrosis (cirrhosis), resulting in blocked intra-hepatic blood circulation (portal hypertension), the consequences of which may be fatal. The importance of fatty infiltration, an almost compulsory consequence of alcohol abuse, should be emphasized ; although reversible, it nonetheless causes functional impairment of the liver in the then abstinent individual. However, long before any of these dramatic complications develop, chronic alcohol intoxication disturbs all of the metabolisms - of carbohydrates, proteins, lipids and vitamins - so that alcoholics rapidly become malnourished. This is all the more frequent since chronic alcoholism often damages the stomach and intestine, causing malabsorption problems, and furthermore, because chronic alcohol intoxication is the main cause of chronic pancreatitis.

**Nutritional importance**

Alcoholics are undernourished, not only because they eat very little (they are anorexic), but above all because their protein synthesis is disturbed and they have vitamin deficiencies (especially in vitamins B and C). Lowered synthesis of coagulation factors may also cause serious haemorrhaging problems.

Understanding of these biological disturbances has contributed to the more rational nutritional management of hepatic failure in cirrhosis patients. Along with the absolutely imperative need to stop drinking, a hypercaloric diet is recommended, but one that avoids the intake of proteins rich in aromatic amino acids, which may cause brain disease. Multivitamin treatment with vitamins B1, B6 and PP in particular, is given as well. In case of ascites, sodium intakes are reduced.

## THE LIVER AND VITAMINS

The liver does not produce any vitamin, of course, since vitamins are by definition molecules which, although necessary for the life process, cannot be synthesized by the human organism. It nonetheless plays a major role in the metabolism of vitamins, since it is able to store a number of them (the fat-soluble vitamins, in particular), and to ensure their regular distribution to those tissues that need them. We will confine our discussion to three fat-soluble vitamins : retinol (vitamin A), calciferol (vitamin D) and phylloquinone (vitamin K).

### Vitamin A

Vitamin A (or retinol) plays an essential role in maintaining satisfactory trophicity in the epithelia of the organism (the intestinal, bronchial, cutaneous and conjunctival epithelia) : it activates the proliferation and differentiation of the epithelial cells, as well as the multiplication of the mucus cells in the secretory epithelia.

Vitamin A is found in food in two forms : either as retinol, preformed in animal foods, or in certain plants, in the form of a

precursor, beta carotene, which is converted into retinol in the intestine. Uptake of retinol is subordinated to its combination (esterification) with a fatty acid, palmitic acid ; this means that uptake of this vitamin requires the presence of a modicum of lipids in the dietary ration. Retinol palmitate is then bound to the chylomicrons, which carry it to the liver. Upon arrival in the hepatic cells, retinol is stored in a receptor protein : retinol storage capacity therefore depends on the amount of protein synthesized, and cannot exceed a certain quantity.

The fact that vitamin A may be stored enables children to survive for several months despite low vitamin A intakes, without showing any clinical signs of xerophthalmia. The amount of stored retinol is believed to enable small children to survive for 6 months without any other supply of the vitamin. Conversely, if retinol intakes are in excess of the storage capacity, as in the case of repeated administration of high doses of vitamin A, the blood retinol concentration rises, and signs of toxicity may develop.

The retinol stored in the liver is used by the peripheral tissues as needed. However, this requires that it be bound again to a plasmatic carrier protein that is also synthesized by the hepatocytes : the retinol binding protein (or RBP). Its synthesis requires sufficient intake of amino acids. In case of severe deficit in proteins, and therefore in amino acids, RBP is insufficiently synthesized, and its blood concentration drops sharply : as a consequence, vitamin A is no longer transported to the peripheral tissues, and to the corneal epithelium in particular, causing signs of xerophthalmia.

**Nutritional importance**

**Vitamin A deficiency (xerophthalmia) in small children is most often linked with inadequate intakes aggravated by repeated infections (particularly measles and diarrhoea). In some cases it may be caused by insufficient hepatic storage, as is occasionally the case in prematures, during pregnancy and especially in kwashiorkor with fatty infiltration of the liver. This deficiency may also be accentuated by insufficient lipid intake, since fatty acids are required for the uptake of this vitamin.**

**It is possible to take advantage of the hepatic storage mechanism to administer vitamin A from time to time to children with a deficiency : a dose of vitamin A may be given every 6 months, for instance.**

**However, synthesis of the retinol binding protein requires sufficient dietary consumption of amino acids. In case of protein energy malnutrition, the administration of vitamin A cannot in itself prevent the development of xerophthalmia : complementary protein intake is required.**

## Vitamin D

Vitamin D, the key vitamin for the metabolism of calcium and phosphorous, is present in the diet in the form of cholecalciferol (vitamin D3). Like vitamin A, it requires the mediation of chylomicrons for uptake. Satisfactory bile secretion is necessary for its absorption, which is impaired, then, during chronic biliary obstruction, which disturbs the emulsification of fats.

Only small amounts of vitamin D are supplied by the diet : the rest is synthesized under the skin through the intermediary of ultra-violet rays. When it arrives in the liver it is transformed into 25 hydroxycholecalciferol (25 OH D3) under the influence of an enzyme that is only found in the liver. 25 OH D3 is fat-soluble, and is stored in the liver as well as in fatty tissue. It has a half-life of about 20 days, and like vitamin A it is exported and transported in the blood stream by a carrier protein. The blood 25 OH D3 concentration is easy to measure. It drops in case of rickets. However, this 25 hydroxy-cholecalciferol is actually not the active form of the vitamin. To perform its function as a vitamin, this molecule must undergo a second hydroxylation in the kidney, which transforms it into 1-25 OH D3, the only form that is active in the metabolism of calcium and phosphorous.

Most fortunately, deficient hepatic 25 OH hydroxylase is unknown in children, whereas impaired renal 1-25 OH hydroxylase does exist, and is responsible for what is known as vitamin-resistant rickets ; in prematures, however, rickets caused by delayed maturation of this enzyme may be seen.

**Nutritional importance**

**The prevention of infantile rickets primarily calls for the regular (daily) administration of small doses of vitamin D3. However, if there is a risk of poor compliance, the intermittent administration of large doses is feasible, given the possibility of storage in the liver and fatty tissues.**

**Intoxication by vitamin D is exceptional, given the two enzyme phases that limit and control its transformation into the active form. This protective mechanism, preventing overdoses, is indispensable, since an excess of the active form would produce hypercalcaemia (through an increase in the digestive uptake of calcium and in its resorption by the bones), potentially highly prejudicial to the child.**

## Vitamin K

Vitamin K is the co-factor of vitamin K-carboxylase, an enzyme that binds a COOH radical to the glutaminic acid present in the V, VI, IX and X coagulation proteins. This simple carboxylation enables these proteins to bind calcium, and thus to begin the formation of a fibrin clot

Vitamin K is naturally present in most edible plants, but it is also synthesized by the bacterial flora, thanks to which the human organism is protected against possible deficiencies (remember the Eskimo problem). It is absorbed with the dietary lipids (like the two forementioned vitamins) and reaches the liver where it acts as a co-factor in the hepatic synthesis of coagulation factors.

In cases of vitamin K deficiency, coagulation disorders develop, with diffuse bleeding. In infants, it produces the haemorrhagic disease of the newborn ; in adults, this deficit occurs occasionally when fat absorption is disturbed by the absence of bile salts (or cholestasis).

**Nutritional importance**

The neonate has very low hepatic reserves at its disposal, and above all, its bacterial flora does not synthesize much vitamin K, so that the administration of vitamin K is indispensable for the prevention of haemorrhagic disease of the newborn.

Given its role as co-factor rather than as an active principle, and the lack of storage in the body, there is no risk of overdose or of toxicity connected with vitamin K.

**Clinical importance**

In adults, decreased or arrested bile secretion (cholestasis) causes malabsorption of fats, and concomitantly, of vitamin K. This results (rarely, in fact), in haemorrhaging, which may be corrected by the parenteral administration of vitamin K. Vitamin K deficiency-linked bleeding is mostly seen in cases of cirrhosis.

## THE LIVER AND THE METABOLISM OF IRON

Although iron is present in the bone marrow, the spleen, the blood (in the form of haemoglobin) and also in many tissues (in the form of myoglobin and cytochromes), it is the liver, with its reserve of up to 1,500 mg in an adult with a normally iron-rich diet, that constitutes the main bodily iron reservoir. This iron is located in the hepatocytes, bound to a protein : ferritin. The iron leaves the liver as it is needed for haematopoiesis, and travels to the bone marrow on a carrier protein : transferrin. Some of the iron is excreted into the intestine by the bile, as well as by the desquamation of the intestinal cells.

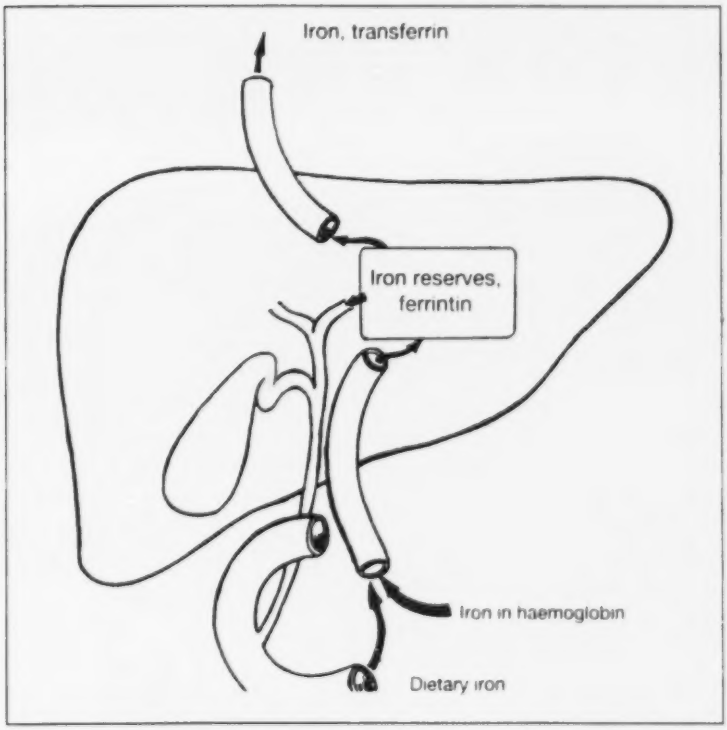


*Figure 11 : Metabolism of iron*

*The liver receives iron from food and from the degradation of haemoglobin. This iron is stored in the liver on a protein : ferritin. When iron is needed by the body, it is released from the ferritin and enters the bloodstream bound to a carrier protein : transferrin.*

The ongoing reconstitution of the body's red blood cell capital requires that the hepatic reserves be refilled correctly. Two mechanisms are involved in this refilling : first, the recycling of the iron supplied by the degradation of haemoglobin, and secondly, the absorption of some of the iron contained in the diet.

**Nutritional importance**

The above description clearly shows that iron deficiency - and the resulting anaemia - is the outcome either of excessive blood loss through bleeding or repeated pregnancies, or of a lack of assimilatable iron in the food ration.

Iron deficiency is extremely frequent in small children, especially when the mother herself suffered from iron deficiency during her pregnancy, or if the child was born before term. Prematures are often iron-deficient because the active uptake and storage of iron is greatest during the last weeks of gestation : it is estimated that 20 % of the newborn's iron reserves are built up during the last two weeks of gestation. This reserve is very important for the first six months of the child's life, since breast milk contains relatively little iron.

**Clinical importance**

An excess of iron in the body is called haemochromatosis. Within the liver, it produces firm hepatomegaly and fibrosis, a possible complication of which is cirrhosis. This is a hereditary ailment causing increased intestinal uptake of iron and hyperavidity for iron in the hepatocytes.

Treatment primarily involves blood letting ; an iron-poor diet is useless, since the inconvenience of a year of dieting may be avoided simply by performing two or three blood lettings.

# TROPICAL INFANTILE LIVER PATHOLOGY

In children living in the tropics, the liver is exposed to the action of many agents that may impair its functioning. These agents are extremely varied, since they include bacteria as well as parasites, viruses, toxins and hepatotoxic drugs, but also nutritional deficiencies. Despite their highly variable nature, these harmful agents elicit relatively identical responses in the liver cells. Examination of a liver specimen (taken by biopsy) consistently shows more or less marked destruction of these cells (necrosis), infiltration by inflammatory cells and the formation of fibrous tissue. Glycogen is often replaced by droplets of lipid (steatosis). Regeneration cells (regeneration nodules) may develop if the aggression is not too intense from the outset. These anomalies finally produce a hard (cirrhotic) liver with a smooth or irregular (studded-looking) surface, generally normal-sized but occasionally small (in atrophic cirrhosis).

Once again, it must be recalled that the liver is remarkably capable of adaptation ; that is, it is able to make the most of the possibilities of those cells that are still intact, and to accelerate the regeneration of new cells. Parenchymal impairment may affect 70 % of the total functional capacity without disturbing hepatic function test results. Cirrhosis may therefore develop over a number of years without causing any major disorder. However, there comes a time when the impairment is so severe that the liver is unable to sustain a normal metabolism : this is known as hepatic insufficiency.

These general remarks show that children have means of defence when their liver is faced with a toxic aggression of any sort. Anatomical changes (fibrosis or regeneration nodules) take a long time to develop, to the point where complications may not be seen until adulthood.

## MAIN CLINICAL SIGNS

We will now briefly review the clinical signs most frequently seen in the advanced stages of the major liver diseases : that is, jaundice (which may also occur during benign ailments), portal hypertension and hepatic coma.

### JAUNDICE

When the bilirubin concentration in the blood is abnormally high for any reason, all of the body tissues, including the skin and the cornea, take on a yellowish tint. This ailment is known as jaundice (or icterus). Jaundice may be caused by three different mechanisms : destruction of the red blood cells, obstruction of the bile ducts and last, impairment of the hepatic cells themselves.

#### *Haemolytic disease*

Haemolytic disease is caused by the massive destruction of red blood cells. The typical example is an infant with mother-child Rhesus incompatibility. An immunitary mechanism causes the

destroyed red blood cells to release their haemoglobin, which is immediately transformed into bilirubin by the liver. The amounts of bilirubin formed are enormous, resulting in severe hyperbilirubinaemia and extremely visible jaundice.

*Obstructive jaundice*

Obstructive jaundice affecting the bile ducts results from an obstacle impeding the outflow of bile, either in the bile canalicules located within the liver (this is intra-hepatic obstruction), or more frequently, in the extra-hepatic bile ducts (the common bile duct). The obstacle may be a gallstone or a tumour affecting the common bile duct.

*Cellular jaundice*

Cellular (or hepatocellular) jaundice is due to the inability of the impaired hepatic cells to purify the bilirubin in the blood. Cell impairment may be the outcome of a viral infection, as is the case during viral hepatitis or yellow fever (with the amaril virus), intoxication by a chemical (as with carbon tetrachloride or phosphorous) or a medication (such as paracetamol) and quite frequently, in adults, it is caused by alcohol abuse.

The course taken by viral hepatitis depends on the virus involved, as will be seen.

## PORTAL HYPERTENSION

During full-blown cirrhosis, masses of new cells are formed and these accumulate in a disorderly manner, with no respect for the architecture of the liver lobule : these are called regeneration nodules. These cell masses obstruct venous circulation and cause a rise in blood pressure throughout the drainage network of the portal vein, producing several serious consequences.

First, there is a rise in blood pressure in the collateral veins, leading to distension of the walls of the veins in the oesophagus (oesophageal varices) and rectum (haemorrhoids) as well as of the abdominal walls. Oesophageal varices are fragile and break easily, causing life-threatening bleeding.

The second consequence is the accumulation of fluid in the abdominal cavity (ascites), a characteristic occurrence in cirrhosis patients. As the ascites develops, the volume of extra-cellular fluid within the organism decreases ; in response to this drop, the adrenal glands secrete more aldosterone which in turn activates water and sodium retention by the kidneys. This hyperaldosteronism is the cause of generalized oedema in cirrhosis patients. The latter therefore suffer from both ascites and peripheral oedema.

There is also a third possible consequence : the regeneration nodules may obstruct the intra-hepatic bile ducts, causing bilirubin to enter the blood stream and producing jaundice. As opposed to the benign jaundice seen in viral hepatitis, which is susceptible of spontaneous recovery, jaundice in a cirrhosis patient is a sign of the uncontrolled - and uncontrollable - progression of the disease.

## HEPATIC COMA

The hepatic coma, a formidable complication of severe liver damage, is produced by an intoxication of the nervous system by ammonia. This ammonia is mostly the product of protein digestion

in the intestine by the bacteria in the colon. During major hepatocellular insufficiency, the liver is unable to detoxify ammonia : this leads to intoxication of the brain centres and a coma known as the hepatic coma.

Hepatic coma may develop following gastro-intestinal bleeding, which increases the amount of proteins in the intestine, or as an aftermath of practically any infection or even of surgery.

The first symptoms, indicating that a coma is imminent, are mental disorders : the patient seems confused, has a distant gaze, and is somnolent during the day and agitated at night. Involuntary movements, with flexing and extension of the fingers, are the result of brief interruptions of muscle tone. Occasionally a characteristic hepatic odour is noted (foetor hepaticus), similar to the smell of freshly cut grass, acetone or aged wine. At a more advanced stage, severe impairment of conscience develops : the patient is completely disoriented in time and space ; then, as the disease progresses, a true coma sets in. The occurrence of encephalopathy indicates that the cirrhosis has entered the terminal phase, inasmuch as there are hardly any therapeutic possibilities at this point.

## THE MOST FREQUENT PAEDIATRIC LIVER DISEASES

The most frequent hepatic disorders occurring in children living in the tropics include viral hepatitis, abscess of the liver, hepatic cirrhosis, tumours of the liver and hepatic disorders connected with protein energy malnutrition. They will be discussed in that order.

### VIRAL HEPATITIS

In children, the symptoms of this liver ailment are loss of appetite with nausea, asthenia, abdominal pain and fever. The temperature returns to normal within 3 to 7 days and jaundice develops. Itching (pruritus) is occasionally seen. It is linked to the presence of bile salts in the blood. Because there is reduced passage of bile pigments into the intestine, the faeces are discoloured and become whitish, while the urine darkens since the pigments are evacuated by the kidneys. Clinical examination shows slight enlargement of the liver. Laboratory findings reveal high transaminase levels (for ASAT and ALAT), exceeding 10 or 100 times the normal figures. The signs of cholestasis are more or less pronounced, and the bilirubin concentrations are high in case of jaundice. Five viruses responsible for viral hepatitis have been identified at present : the A, B, C, D and E viruses.

#### Hepatitis A

The hepatitis A virus is responsible for epidemics that mainly affect children and young adults. In developing countries, most of the population (80 to 90 %) is exposed to this virus before age 10 years. Transmission to children occurs via water and food contaminated by faecal matter. Hygiene is therefore primordial, conditioning the occurrence of the disease.

The incubation period lasts an average of 4 weeks. In children, the infection is often not very marked, clinically speaking, and recovery occurs within several weeks.

There is no specific treatment for hepatitis A. On the other hand, prevention is now feasible, thanks to a vaccine containing the inactivated A virus : two injections are required, at a 1-month interval, with a booster one year later. Post-vaccinal immunity probably lasts more than ten years. Immunity subsequent to natural disease is stable and lasting.

**Hepatitis B**

It is estimated that over 300 million individuals around the world are carriers of the B virus (HB virus). There are tremendous geographic variations in the frequency of its presence : it is low in the western world and peaks in Africa ; in Senegal, for instance, 80 % of children have been in contact with the B virus by age 13.

Transmission may be parenteral, percutaneous, perinatal or sexual. Blood from an infected individual is the point of departure of transmissions by the parenteral or percutaneous route. At-risk individuals are mostly drug abusers, haemodialysis patients and personnel working in hospitals or in laboratories doing medical testing. Transmission by the transfusion of blood or blood plasma has been reduced considerably since the introduction of routine testing of blood donors for the viral antigen (the HBs antigen).

Neonates born to contaminated mothers represent another at-risk group. Since this virus does not cross the placental barrier, transmission probably takes place during delivery : in those parts of Africa and Asia where endemicity is high, this is the usual type of contamination.

The incubation period averages 75 days. Hepatitis B may take a number of quite different clinical forms : it may be symptom-free, especially after perinatal transmission, be similar to a bout of influenza, with no jaundice (in 65 % of cases), be a classical icterogenic case of hepatitis (30 %) or last, be immediately fulminant (1 %). Diagnosis is based on clinical findings, the evidencing of a marked increase in transaminases and the isolation of vital antigens, followed by the corresponding antibodies, in the blood. The disease may last for two to six weeks.

In 1 % of patients, the development of this hepatitis is fulminant. Within a few days, hepatocellular insufficiency develops, with hepatic encephalopathy. Before the introduction of liver transplantation, the outcome was generally lethal. Last, in 5 to 10 % of patients, hepatitis B becomes chronic. This latter course is to be feared, since chronic viral hepatitis is susceptible of progressing to cirrhosis, with a major risk of occurrence of a hepatocellular carcinoma (see below).

There is no specific treatment for B type acute hepatitis. Passive immunization by the administration of specific gamma globulins is effective in individuals suspected of recent contamination. Active immunization by the vaccination of all at-risk individuals is strongly recommended ; vaccination of neonates born to contaminated mothers should be performed within hours of birth.

**Hepatitis C**

The hepatitis C virus, recently discovered, is responsible for most cases of non-A non-B hepatitis, transmitted parenterally. This means that C virus hepatitis may only be suspected in a child who has been transfused. Like the B virus, the C virus is very unevenly distributed around the world. Prevalence of C virus hepatitis ranges from 1 to 2 % in Europe, while in Africa the figure is 1 % in Niger, for instance, and 10 % in Central Africa.

In adults, this form of hepatitis is predominantly asymptomatic, and frequently becomes chronic. 50 % of patients with acute hepatitis C progress spontaneously to recovery, whereas approximately half of the 50 % who are chronically ill develop cirrhosis, and 10 % develop a hepatocellular carcinoma.

**Hepatitis D**

The D virus, also called the Delta virus, is only pathogenic in conjunction with the B virus. Transmission is primarily parenteral, involving contaminated blood or blood products. Like the B virus, the D virus is endemic in tropical and subtropical regions, and the clinical picture is similar to that seen in acute hepatitis B.

**Hepatitis E**

The hepatitis E virus rages in endemic/epidemic fashion in areas where personal hygiene is faulty. In Senegal, over 10 % of cases of acute hepatitis are caused by the E virus. Epidemics, which are frequent in the tropics, affect young adults and are responsible for many deaths from fulminant hepatitis in pregnant women.

This review of the various forms of viral hepatitis and its causal agents clearly shows that acute hepatitis is usually benign, and that there is no treatment for it. On the contrary, the administration of drugs should be avoided whenever possible, since hepatic metabolism of drugs may be considerably impaired during hepatitis, and the toxicity of any medication may be enhanced.

It is important, above all, to recommend simple measures of hygiene to avoid contaminating people in contact with a patient (especially in hepatitis A and E, where transmission may be faeco-oral), and to unhesitatingly protect close contacts : in hepatitis A, by the injection of non-specific immune globulins and in hepatitis B and hepatitis D, by the injection of specific anti-HB immune globulins along with vaccination.

## ABSCESS OF THE LIVER

Whenever any infection develops in the digestive track, there is a risk that the portal venous system will carry an infectious embolus, or plug, to the liver, where an abscess may develop. The most frequent infectious agents in tropical areas are amoebas (essentially, Entamoeba histolytica, the agent of amoebic dysentery) and more exceptionally, gram-negative bacilli (Escherichia Coli) and anaerobic bacteria. Furthermore, during septicaemia, micro-organisms may reach the liver through the hepatic artery, producing multiple abscesses of the liver. Fortunately, most bacteria are destroyed rapidly, but some may occasionally elude the means of defence. The micro-organisms produce toxins that destroy the surrounding liver cells, and the necrotic tissue thus produced then becomes a protective nest for the pathogenic organisms. In the meanwhile, the leukocytes reach

the infected area. The result is the constitution of an abscess filled with a fluid containing live and dead leukocytes ; in amoebic abscesses this pus is chocolate-coloured.

Abscesses generate systemic signs, including fever with shivering and jaundice, and local signs : painful hypochondrium with irradiation to the back. The liver is enlarged, and painful to the touch. Formerly, abscesses of the liver were fearsome, but satisfactory medical treatment is now available in the form of antiparasitic agents in amoebic involvement (metronidazole), or, when pyogens are involved, prolonged antibiotherapy completed when necessary by puncture to drain the abscess.

## CIRRHOSIS OF THE LIVER

Cirrhosis is the expression of scar formation in the liver. It may take three forms in adults :

- Laennec's cirrhosis, in which the portal spaces are characteristically surrounded by fibrous tissue. Use of alcohol is the chief aetiological factor in this type of cirrhosis ;

- post-necrotic cirrhosis, characterized by the presence of large bands of sclerotic tissue ; it is an aftermath of earlier viral hepatitis having caused local tissue necrosis ;

- biliary cirrhosis, with sclerosis of the interstitial tissue of the portal and interlobular spaces. This form is the outcome of chronic biliary obstruction and of infection (inflammation of a bile duct), and is much more exceptional than Laennec's cirrhosis and post-necrotic cirrhosis.

Fortunately, small children never develop cirrhosis of alcoholic origin or biliary cirrhosis, the latter being almost exclusively observed in adult women aged 40 to 60. Some cases of cirrhosis of viral origin may be seen, however, and their incidence is correlated with the prevalence of the viral markers in the population. In Africa and Asia, the primary cause is the B virus.

Cirrhosis progresses in three phases, grossly speaking. The first and often longest phase is symptom-free. The second is marked by the development of asthenia, and impaired general health. In the third phase there is development of complications connected with the hepatic insufficiency and portal hypertension : ascites, digestive haemorrhaging and encephalopathy.

It should be remembered that a number of diseases of genetic origin may cause cirrhosis in children. These include haemochromatosis, characterized by the abnormal accumulation of iron in a number of organs including the liver, Wilson's disease, caused by a hereditary anomaly in the metabolism of copper, alpha-1-antitrypsin deficiency, which may produce cholestatic hepatitis and possibly even hepatic fibrosis in homozygous neonates, and last, mucoviscidosis. Hereditary diseases such as glycogenosis, galactosaemia and fructosaemia, affecting the metabolism of carbohydrates, may also result in rapidly progressing cirrhosis in infants. Fortunately, these ailments are exceptional.

## TUMOURS OF THE LIVER

The tumours of the liver observed in children in the tropics may be either benign or malignant (cancers). The most frequent benign tumour with a liquid content is the hydatic cyst, particularly prevalent in some parts of the world. Malignant tumours include some cases of primitive cancer of the liver, or hepatocarcinoma, but luckily these are exceptional in children under age 10.

### Hydatic cysts

Hydatic cysts are caused by the development of the larva of Echinococcus granulosus, and are mostly encountered in sheep-raising country. Cows, sheep and human beings are the intermediate hosts of this parasite, the final hosts being dogs. People are infected by ingesting parasite eggs evacuated in the dejections of a contaminated dog. The eggs cross the intestinal mucosa and travel to the liver through the portal vein. Most hydatic cysts are therefore located in the liver. Often these cysts do not produce any symptoms, and are discovered only by accident. There is not necessarily enlargement of the liver. The hepatic enzymes are normal. Isolation of specific antibodies in the blood yields an affirmative diagnosis ; this test may be negative, however, especially if the parasite is dead. Often these cysts are discovered during an x-ray and even more frequently, during ultrasonography. Treatment is primarily surgical, and involves removal of the cyst, since it may cause complications - rupture of the cyst, compression of neighbouring organs, etc. - if allowed to develop.

### Primitive cancer of the liver, or hepatocarcinoma

Hepatocarcinomas occur everywhere in the world, but their incidence is extremely variable : it exceeds 50 cases annually per 100,000 inhabitants in black Africa and South-East Asia, while it ranges from 32 to 35 per 100,000 in Europe and the USA. Chronic infection with the B virus and ingestion of aflatoxin - a toxin secreted by a mold - are known aetiological factors.

There is a correlation between the prevalence of viral infection and the annual incidence of this tumour in various countries. The risk of cancer is multiplied by a factor somewhere between 7 and 100, depending on the group studied, for carriers of the HBsAg antigen. As a rule, contamination occurred more than 20 years earlier, and cirrhosis developed before the cancer was seen. This means that hepatocarcinoma is an exceptional occurrence in children under age 10.

Aflatoxin, produced by a mold (Aspergillus flavus) that develops on seeds (especially peanuts) stored in a hot, humid atmosphere, induces hepatic tumours in animals. In human pathology, it may act as a co-carcinogen in association with the hepatitis B virus.

Clinical signs of primitive cancer of the liver include impairment of general health and hepatomegaly, with an irregular, enlarged, sensitive liver. Once it has developed, this cancer progresses rapidly, and treatment is unfortunately rather ineffectual.

Prevention of hepatocarcinoma involves immunization against the hepatitis B virus and the identification of blood donors carrying the hepatitis C virus.

In conclusion to this chapter on liver diseases in children in the tropics, emphasis should be placed on the variety of pathogenic agents involved. These range from viruses (in viral hepatitis) to carcinogens (for hepatocarcinomas), and include parasites (in hydatic cysts). Furthermore, the clinical signs are rarely sufficient, in themselves, to point to an aetiological diagnosis and therefore to determine treatment. The physician who cannot rely on any data other than clinical signs for diagnosis is often faced with great difficulties, then ; laboratory tests and investigation techniques - such as ultrasonography - would be necessary, but in some parts of developing countries these are unfortunately not always available.

## IMPAIRMENT OF THE LIVER AND MALNUTRITION IN CHILDREN

Childhood malnutrition is above all the result of insufficient intakes of energy and amino acids ; these intakes are essential for the synthesis of proteins, which is particularly active during this period of growth. Any such deficiency affects all of the organs, but especially the digestive organs, including the intestinal mucosa, the pancreas and of course, the liver.

In the past, observers were intrigued by the hepatic signs seen in the course of kwashiorkor. Quite unexpectedly, the autopsy of children who had died of kwashiorkor revealed hepatomegaly, with a sometimes enormous liver and fatty infiltration, impossible to suspect in these excessively thin children.

Histologic examination showed an accumulation of droplets of fat, located at first on the outskirts of the lobule, and then, as these lipid deposits increased in size, infiltrating the central region of the lobule. In the most severe cases, the totality of the hepatic cells are filled with a vast lipidic vacuola that forced the nucleus back and compressed the cytoplasm. The accumulated lipids were composed of triglycerides. The first observers were also surprised to discover that in spite of this massive fatty infiltration, the hepatic functions were maintained, and that severe hepatic insufficiency was exceptional. Bilirubin concentrations were normal, the prothrombin concentration was often low, but returned to normal following the administration of vitamin K. For many years, then, the medical corps wondered about the causes of this anomaly, so specific to kwashiorkor and never seen in children with marasmus.

The role of protein deficiency in the fatty overloading of the liver was definitely established with the evidencing of the role of VLDL lipoproteins as carriers of triglycerides from the liver to the periphery. It then became clear that the anomaly was linked to faulty synthesis of VLDL lipoproteins, owing to an amino acid deficiency.

Likewise, during rehabilitation of children with kwashiorkor, the administration of proteins brings the serum lipoprotein concentration back to normal, and the volume of the liver then gradually recedes, returning to normal after several weeks. In most cases, the cells retrieve their normal histological appearance and recovery occurs with no fibrosis.

Nonetheless, the occurrence of hepatic anomalies which may reach the point of cirrhosis, sometimes called «nutritional cirrhosis» despite the lack of proof, is not exceptional in adolescents and adults living in third world countries where childhood malnutrition is endemic. Many writers suspect that these individuals, whose liver suffered from protein energy malnutrition often associated with vitamin and mineral deficiencies during their childhood, are particularly susceptible to the action of infectious agents such as viruses or chemical agents such as mycotoxins or alcohol ; later, as adults, they tend to develop chronic liver ailments more easily. Numerous experimental studies conducted on animals seem to corroborate this hypothesis.

## LIVER AILMENTS IN PREGNANT WOMEN

The occurrence of liver disease during pregnancy is always a problem, since it is a source of risk for the expectant mother and may affect the foetus. A clear distinction must be made, from this point of view, between liver diseases strictly connected with pregnancy, on the one hand, and cases of hepatitis occurring during pregnancy on the other hand, since the prognosis is not the same.

### Benign hepatic jaundice

The most frequent hepatic ailment connected with pregnancy is known as benign hepatic jaundice. It occurs during the 2nd and 3rd trimesters of pregnancy, and its prevalence varies from country to country : about 15 % in Chile, 2 % in Sweden and 0.5 % in France, to take a few examples. It produces simple itching, with no fever, weight loss due to a restricted diet, and possible depressive disorders. The itching is often - but not necessarily - followed by jaundice. The hepatic lesions are typical of pure cholestasis. The mechanism is unclear, but the gestational steroid hormones seem to be involved in the development of this jaundice. Itching generally disappears two or three days after delivery. While the prognosis for the mother is good, premature delivery does occur in 30 % of cases. Recurrence of the ailment during a subsequent pregnancy is frequent (whence another name for it : recurrent gestational jaundice) but not constant. Since there is no medical treatment, the pregnancy is often terminated by caesarean section at about 8 months.

### Acute steatosis of the liver

Acute steatosis of the liver is an extremely rare ailment occurring during the last three months of pregnancy. The clinical picture includes jaundice, along with intense vomiting during the pre-icteric period and haematemesis during the jaundice phase. This results in death of the foetus in utero or during premature delivery, often followed by death of the mother. The mechanism is still unclear ; there is no effective treatment except for a liver transplant.

### Jaundice concomitant with pregnancy

Jaundice caused by viral hepatitis, although unconnected with pregnancy, occurs relatively frequently in association with it. The viral agents may be the A, B, C, D and E viruses and the herpes virus. All of these types of hepatitis are conducive to prematurity and increase foetal morbidity.

The course taken is benign for the mother, as a rule. However, severe hepatitis may develop, especially in multiparas and malnourished mothers. This is what is known as fulminant hepatitis, with superacute, rapidly progressing hepatic insufficiency and acute atrophy of the liver, resulting in death of both mother and child, despite treatment of the hepatic coma.

Any liver ailment occurring during pregnancy therefore requires that every effort be made to determine the cause, and to evaluate the risk of a negative effect on the pregnancy as well as the risk of recurrence during a subsequent pregnancy.

## CONCLUSION

The liver plays an active role in all of the major metabolic processes : in the metabolism of carbohydrates, proteins and lipids, as well as of many vitamins and several minerals necessary for the proper functioning of the body. It supplies the tissues with the nutrients they require, in an appropriate form - one that is easily metabolizable by the utilizing tissues - and in adequate amounts. Thus, the liver adjusts its nutrient production to the daily fluctuations in the needs of the organism. In the growing child, it adjusts its ability to synthesize amino acids and proteins to the specific needs of that time of life. Its functioning is so well regulated that it may adjust to dietary regimens as varied as the carbohydrate-based diet of Asian children and the lipid and protein-based diet of young Eskimos. It is thanks to the liver that people are not obliged to eat constantly, day and night. This leaves them time to search out or earn their food, and enables them to tolerate long periods of fasting without any damage to the functioning of their brain.

Furthermore, the liver is able to react to and to cope with the metabolic needs of the organism threatened by infectious diseases, burns or other aggressions by synthesizing, as needed, the proteins required for tissue repair.

The liver is also our best ally against toxic aggressions by the environment, since it possesses innumerable means - the detoxification enzymes - of ridding the organism of these poisons, as well as an exceptionally developed capacity to react to aggressions, thanks to the unusual regenerative ability of the hepatic cells.

Nonetheless, these reactive capacities are not unlimited, by any means. When they are outdistanced, because the aggression is either excessively violent or too prolonged, the consequences rapidly become dramatic for the individual, since the liver is the only organ in charge of certain functions.

**The liver may therefore be said to be the key organ for nutrition.**

In this context, the question then arises : is there an ideal dietary regimen, capable of maintaining hepatic functions at an optimal level and perhaps even for the longest possible duration ? It is true that the liver is very well equipped to cope with major fluctuations in daily intakes of proteins, carbohydrates and lipids. However, physiological investigations have shown the existence of an optimum, to be respected in intakes of these three broad

categories of nutrients. It is this optimum that is referred to as a balanced diet. Concretely, it is estimated that for a diet to be balanced, proteins should represent an average of 12 % of the daily caloric intake, lipids 35 % and carbohydrates 50 to 55 %. These are average figures, of course, meaning that divergence from these figures for intake are inconsequential, provided they do not occur too repeatedly. Conversely, a diet regularly containing too much carbohydrate (and therefore too little lipid), as well as one that is consistently hyperlipidic (and therefore poor in carbohydrates) may cause disturbances over the long term. Likewise, it is now well known that low protein diets are extremely harmful, especially for growing children, and the same is true of an imbalance in micronutrients.

Thus, our understanding of the biochemical functioning of the liver corroborates the findings of physiological studies, and justifies those recommendations for a balanced diet presently advanced by nutritionists.

Moreover, our understanding of the mechanisms behind the action of toxins and other chemical agents within the liver also justifies the norms prescribed by the international agencies - such as the Codex Alimentarius FAO/WHO norms - for the levels of food contamination not to be exceeded.

Last, a reminder about alcohol. This is the toxic agent most frequently consumed by human beings - often starting at an early age, alas - and the liver is the only organ that works at detoxifying the body of this substance, while at the same time, it is called upon to do so for many medications, uncontrolled environmental toxins, etc. Which is to say that it is not superfluous to recommend caution in the consumption of alcohol.

Gradually, then, we have gained perspective on guidelines for a «wise diet», one that would spare the liver as much as possible. It is based on a dietary balance in macronutrients as well as in micronutrients, and contains as few toxins - including alcohol - as possible.

**The liver may be said to be our best friend, then, where our nutritional status and health are concerned : but there is also a saying that one should respect his or her friends, and not demand too much of them.**

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# FOR FURTHER INFORMATION...

## Glossary of terms employed

### A

***ascites***
presence of fluid in the abdomen

***aflatoxin***
cancerous toxin secreted by a mold, the Aspergillus flavus

***antigen***
substance inducing the development of antibodies in the organism

***antibody***
a protein substance combating the action of an antigen

### B

***bile pigment***
bilirubin

***bilirubin***
reddish-yellow substance produced by the degradation of haemoglobin

### C

***catabolism***
phase in the metabolic process by which organic compounds are degraded, and energy is produced

***carcinoma (hepatocellular)***
cancer of the hepatic cells

***cholestasis***
arrested bile flow

***cirrhosis***
word coined by Laennec to designate the disease in which the liver develops tawny granulation. By extension, a pathological anatomic process in the liver, characterized by the proliferation of a fibrous conjunctival-vascular tissue that encloses and mutilates the hepatic parenchyma

### D

***detoxification***
mechanism by which a substance loses its toxicity

### E

***enzyme***
protein molecule capable of accelerating a particular chemical reaction

***epithelium***
cellular lining delimiting the periphery (the skin) or the cavities of the body

### F

***ferritin***
protein representing the storage form for iron within the body

### H

***haematemesis***
vomiting of blood

***haemochromatosis***
anomaly of the metabolism of iron, resulting in diffuse cellular overload with ferritin and haemosiderin in various tissues, and especially in the liver

***hepatitis***
any inflammatory infection of the liver

***hepatomegaly***
enlargement of the volume of the liver

***hepatocyte***
hepatic parenchyma cell

***hepatocarcinoma***
malignant tumour, cancer of the liver

***hyperbilirubinaemia***
high blood bilirubin concentration

## I

***icterus***
more or less intense yellow colouring of the teguments and mucosa, owing to the impregnation of tissues by the bile pigments. Synonym : jaundice

## K

***ketonic bodies***
chemical bodies formed from certain amino acids and lipids

***Kupffer's cells***
large, star-shaped cells present in the liver, and belonging to the endothelial lining of the sinusoidal capillaries

***kwashiorkor***
form of malnutrition seen in small children, combining low weight and the presence of oedemas

## L

***lipoproteins***
a molecular combination of proteins and lipids ; most of the blood lipids are serum lipoproteins

## M

***macrophages***
cells capable of swallowing and destroying germs or damaged cells

## N

***neoglucogenesis (or neoglycogenesis)***
formation of glycogen in the liver

***nutrient***
food that does not need to be digested to be assimilated by the body

## O

***oedema***
infiltration with fluid, susceptible of affecting different parts of the body including the subcutaneous tissue of the lower limbs

## P

***parenchyma***
the functional tissue of an organ or gland (as opposed to the conjunctival, supportive tissue)

***pruritus***
cutaneous itching, linked to the presence of bile salts in the blood

***pyogens***
bacteria causing pus formation

## S

***serum***
part of the blood that remains liquid after coagulation

***spleen***
lymphoid organ weighing about 200 grams, situated in the left subphrenic space

***splenomegaly***
enlargement of the spleen

***steatosis***
abnormal accumulation of fat in the cells

***syndrome***
a set of clinical signs or symptoms commonly occurring at the same time in the course of a disease

## T

***transaminases***
enzymes inducing transamination : chemical reactions making the synthesis of certain amino acids possible

***triglyceride***
a type of lipids, a neutral fat composed of glycerol and three fatty acids

***transferrin***
protein present in small amounts in the blood plasma, the function of which is the reversible binding of iron and its transport to the tissues

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*"A meal at the marketplace". Picture by Doctor Michel CHAULIAC (Cambodia).*

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